

UNIVERSITY OF BIRMINGHAM

Research at Birmingham

Oral antimicrobial peptides

Khurshid, Zohaib; Naseem, Mustafa; Sheikh, Zeeshan; Najeeb, Shariq; Shahab, Sana; Zafar, Muhammad Sohail

DOI:

[10.1016/j.jsps.2015.02.015](https://doi.org/10.1016/j.jsps.2015.02.015)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Khurshid, Z, Naseem, M, Sheikh, Z, Najeeb, S, Shahab, S & Zafar, MS 2015, 'Oral antimicrobial peptides: Types and role in the oral cavity', Saudi Pharmaceutical Journal. <https://doi.org/10.1016/j.jsps.2015.02.015>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

Published under Creative Commons Attribution Non-Commercial, No-Derivatives license - <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Eligibility for repository checked April 2015

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Accepted Manuscript

Review

Oral Antimicrobial Peptides: Types and Role in the Oral Cavity

Zohaib Khurshid, Mustafa Naseem, Zeeshan Sheikh, Shariq Najeeb, Sana Shahab, Muhammad Sohail Zafar

PII: S1319-0164(15)00053-5
DOI: <http://dx.doi.org/10.1016/j.jsps.2015.02.015>
Reference: SPJ 391

To appear in: *Saudi Pharmaceutical Journal*

Received Date: 18 January 2015
Accepted Date: 20 February 2015

Please cite this article as: Khurshid, Z., Naseem, M., Sheikh, Z., Najeeb, S., Shahab, S., Zafar, M.S., Oral Antimicrobial Peptides: Types and Role in the Oral Cavity, *Saudi Pharmaceutical Journal* (2015), doi: <http://dx.doi.org/10.1016/j.jsps.2015.02.015>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Manuscript Number: SPJ 391

Title: Oral Antimicrobial Peptides: Types and Role in the Oral Cavity

Article Type: Review Article

Corresponding Author: Dr. Zohaib Khurshid, BDS; MRes

Corresponding Author's Institution: School of Material and Metallurgy,

First Author: Zohaib Khurshid, BDS; MRes

Order of Authors: Zohaib Khurshid, BDS; MRes; Mustafa Naseem, B.D.S., MDPH; Zeeshan Sheikh, PhD; Shariq Najeeb, B.D.S., MSc; Sana Shahab, B.D.S., MSc; Muhammad Sohail Zafar, Ph.D., M.Sc., B.D.S.

Author's Name:

- 1) Zohaib Khurshid*
- 2) Mustafa Naseem
- 3) Zeeshan Sheikh
- 4) Shariq Najeeb
- 5) Sana Shahab
- 6) Muhammad Sohail Zafar

Author's Affiliations:

- 1) School of Materials and Metallurgy, University of Birmingham, United Kingdom.
- 2) Department of Community dentistry and Preventive Dentistry, School of Dentistry, Ziauddin University, Pakistan.
- 3) Faculty of Dentistry, University of Toronto. Toronto, Canada.
- 4) School of Dentistry, Al-Farabi Dental College, Kingdom of Saudi Arabia.
- 5) Department of Dental Materials Science, Sir Syed College of Medical Sciences for Girls, Pakistan.
- 6) Department of Restorative Dentistry, College of Dentistry, Taibah University, Madinah Al-Munawwarah, Saudi Arabia

Oral Antimicrobial Peptides: Types and Role in the Oral Cavity

Abstract

Antimicrobial peptides (AMPs) are a wide-ranging class of host-defense molecules that act early to contest against microbial invasion and challenge. These are small cationic peptides that play an important in the development of innate immunity. In the oral cavity, the AMPs are produced by the salivary glands and the oral epithelium and serve defensive purposes. The aim of this review is to discuss the types and functions of oral AMPs and their role in combating microorganisms and infections in the oral cavity.

Keywords: Antimicrobial peptides (AMPs); oral cavity; defensins; cathelicidins; histatins; dental applications.

Contents

1. Introduction.....	3
2. Mechanisms of action.....	4
3. Types of oral antimicrobial peptides.....	5
3.1. Defensins.....	5
3.2. Histatins.....	7
3.3. Cathelicidins (LL- 37).....	9
3.4. Adrenomedullin.....	10
3.5. Statherin.....	10
3.6. C-C motif chemokine 28.....	11
3.7. Azurocidin.....	11
3.8. Neuropeptides	11
3.9. Role of AMPs in oral diseases.....	12
4. Conclusions.....	14
References.....	15

1. Introduction

All living organisms have defence systems for combating microorganisms and potential pathogens (Zasloff 2002, Dale, Tao et al. 2006, Cardot Martin, Michel et al. 2015). In the higher vertebrates, prior to the evolution of adaptive immunity, a more simpler and nonspecific system of innate immunity evolved and still continues to play a role as the principal defence system for almost all living organisms (Adonogianaki, Moughal et al. 1993, Adonogianaki, Mooney et al. 1996, Aguilera, Andres et al. 1998). The innate immunity modulates its antimicrobial functionality by small cationic peptides with activity against gram-positive and negative bacteria, parasites, fungi and some viruses (Akalin, Bulut et al. 1993, Allaker, Zihni et al. 1999, Allgrove, Gomes et al. 2008). The mechanism of action against microbes and pathogens is principally attributed to the disruption of the microbial cell membrane (van 't Hof, Veerman et al. 2001, Shai 2002). However, complete understanding of the exact process or processes is deficient and it is plausible that other mechanisms are at play which are yet to be identified (Quinones-Mateu, Lederman et al. 2003, Sinha, Cheshenko et al. 2003, Wang, Owen et al. 2004, Yasin, Wang et al. 2004, Gordon, Huang et al. 2005).

The innate immune system augments the physical and chemical barriers e.g. skin and mucous membranes by producing antimicrobial peptides (AMPs) (Hancock and Sahl 2006). AMPs have a widespread distribution in human body and have antimicrobial activity against microorganisms (Zasloff 2002, Gordon, Romanowski et al. 2005). All AMPs are extracted from larger precursors and comprise of a signal sequence with post-translational modification that includes glycosylation (Sewald and Jakubke 2002), proteolysis (Vos, Kuipers et al. 1995), amino-acids isomerization, carboxy-terminal amidation and halogenation (Bulet, Dimarcq et al. 1993). To date around 106 Human host defense peptides have been identified

(Wang 2014). AMPs are found in oral saliva, in the epithelium and in neutrophils (Dale, Tao et al. 2006). AMPs are classified in different classes according to amino acid composition, size and conformational structures (Table-1) (Hancock and Lehrer 1998, Brogden 2005, Harris, Dennison et al. 2009).

The oral cavity has a very unique environment and microorganisms and pathogens have easy access to it and the rest of the body through epithelium and the gastrointestinal tract (Dale and Fredericks 2005). Despite the high microbial load of the oral cavity that can potentially be disease forming, abrasions, cuts and minor surgical procedures rarely lead to infection. This indicates the highly effective host-defence mechanisms that exist and are active (Zasloff 2002). Oral epithelial cells, salivary glands and neutrophils secrete at least forty five identifiable antimicrobial gene products that are found in saliva. Saliva acts as a potent line of defense owing to its antibacterial, antioxidant and antifungal properties along with the oral mucosa, which plays a role as an important barrier (Amerongen and Veerman 2002, Yoshio, Lagercrantz et al. 2004). The most common AMPs that express in the oral cavity are listed in Table 2. Subsets of these AMPs are also expressed in the crevicular fluid and are more concentrated than in saliva (Alves and Olivia Pereira 2014, Ashby, Petkova et al. 2014). In addition to their role played as antimicrobials, AMPs also serve as effective biological molecules in immune activation, inflammation and wound healing (Yang, Biragyn et al. 2002, Koczulla and Bals 2003, Yang, Biragyn et al. 2004) and are being extensively researched upon for clinical applications (Koczulla and Bals 2003, Dale, Tao et al. 2006, Meyer and Harder 2007, Kang, Park et al. 2014, Vale, Aguiar et al. 2014).

2. Mechanisms of action

Many studies have previously researched and reported the mechanisms of action of AMPs against microorganisms (Vos, Kuipers et al. 1995, Gennaro, Zanetti et al. 2002, Ganz 2003, Brogden 2005, Dale, Tao et al. 2006, Gorr 2009, Melo and Castanho 2012, Tomasinsig, Skerlavaj et al. 2012, Haney, Petersen et al. 2013, Wang 2014). However, the mechanisms most widely accepted are the barrel-stave model, carpet model, and toroidal model for killing organisms. In *barrel-stave model*, peptides position themselves for binding on the cell membranes, this leads to peptide aggregation and conversion to a bilayer membrane. So in this way the hydrophobic peptides align with the lipid core and hydrophilic peptides form an access pore in the interior part of membrane (Figure 1.a). The *carpet model* is described as a disruption of the membrane by binding of peptides to the outer surface (phospholipids) of cell membrane and forming a prolonged layer or carpet (Figure 1.b). In the *toroidal model*, attached peptides start aggregation and force the lipid monolayer to bend incessantly through the pores. In this way the core is lined by both the inserted peptides and the lipid head groups (Figure 1.c) (Epand and Vogel 1999, Bocchinfuso, Palleschi et al. 2009). Types and role of antimicrobial peptides have been discussed here.

3. Types of oral antimicrobial peptides

3.1. Defensins

Defensins are short, cationic, low molecular weight (~4-5 kDa) peptides with ~6-8 cysteine residues which form 3-4 intramolecular disulfide bonds (White, Wimley et al. 1995). Defensins are extensively studied due to their wide expression in human body and the capability to kill all kind of gram-positive and negative bacteria, fungi and as well as viruses such as herpes simplex (Ganz 2003, Wang, Owen et al. 2004, Diamond and Ryan 2011, Wang 2014). Human defensins are classified as α -, β - and θ - on the basis of their length,

location, position of cysteine and folding of peptide chains (Abiko, Saitoh et al. 2007, Greer, Zenobia et al. 2013).

Mature α -defensin family have been isolated from human neutrophils as hNP-1, hNP-2, hNP-3 and hNP-4 (Selsted, Harwig et al. 1985). These neutrophils are nearly identical in amino acid sequences but the N-terminus of hNP-1 end with alanine (Ala) and aspartate (Asp) for hNP-3 (Figure 2). These changes affect defensin antimicrobial spectrum as already reported by *Ganz.et.al.* (Ganz, Selsted et al. 1985). The hNP-3 is less active than hNP-1 or hNP-3 in destroying *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escherichia coli* (Ganz, Selsted et al. 1985). hNP-4 has been researched and identified by *Griffith et al.* by chromatographic methods, as 33 amino acid sequences expressed in neutrophils with activity against *E.coli*, *Streptococcus faecalis* and *Candida albicans* (Wilde, Griffith et al. 1989). The last two family members of α -human neutrophils peptides (hNP-5 and hNP-6) are present in the enteric system and do not express in the oral cavity (Gomes Pde and Fernandes 2010). In a healthy human, hNP-1 to 3 is most abundantly present in saliva (around 99 %). The levels of hNP-4 are roughly 100 folds lower (Gabay, Scott et al. 1989, Gomes Pde and Fernandes 2010). The concentration of hNP-1 is higher in saliva of patients with oral diseases such as lichen planus, leukoplakia and squamous cell carcinoma) in contrast to healthy individuals (Dunsche, Açil et al. 2001). The level of hNP-1, -2 and -3 has been shown to be reduced in edentulous patients due to the absence of gingival crevices (Fanali, Inzitari et al. 2007). *Dale et al.* have reported low salivary levels of α -defensins (hNP-1, -2 and -3) in patients having dental caries and suggested that these are biological factors that can be used for caries risk assessment in general population (Dale, Tao et al. 2006).

The β -defensins family contain six members (hBD-1-6), and principally they are all expressed in epithelial cells that cover several tissues and organs including the skin, mucosal surfaces of oral cavity, respiratory tract, gastrointestinal tract, genitourinary tract, and kidney

(Gorr 2011). The molecular structure of β -defensins is represented in Figure 2. Research has proved that only hBD-1, hBD-2, and hBD-3 are expressed in the oral cavity (gingival epithelia, tongue, palate and buccal mucosae, salivary glands/ducts and saliva) (Dale and Krisanaprakornkit 2001). Human Beta defensins -1 and -2 localized within the suprabasal layer of normal gingiva and hBD-3 peptide is expressed in undifferentiated epithelial cells within the basal layer (Pisano, Cabras et al. 2005). It has been suggested that hBD-1 is continuously expressed and plays a role in the impediment of normal flora from becoming opportunistic. Whereas the hBD-2 and -3 are inducible in response to bacterial lipopolysaccharides (LPS), proinflammatory mediators (Interleukins[IL-1 β], tumor necrosis factors [TNF- α], interferons [IFN- γ]) and are more effective against almost all pathogens (Krisanaprakornkit, Weinberg et al. 1998). These peptides are in low concentration in the gingival crevicular fluid. Immunohistochemistry has been carried out in tissues sample from radicular cyst, lichen planus, leukoplakia and candida leukoplakia suggesting that hBD-2 is forcefully induced by lichen-planus related inflammation and play role in protecting candida albicans (Abiko, Jinbu et al. 2002). Zhao *et al.* reported that the location of human genes for α -defensins and β -defensins are adjacent to loci on chromosome 8p22-p23 (Liu, Zhao et al. 1997).

3.2. Histatins

Histatins are a family of salivary proteins with low molecular weight cationic peptides synthesized by the parotid and submandibular salivary ducts cells at around 50-425 μ g/ml in healthy adults (de Sousa-Pereira, Amado et al. 2013). They are 7 to 38 amino acids residues in length with at least 12 histidine residues, hence called as *histidine rich proteins*. Histatins are predominantly antifungal and comprise of three main members (His-1, His-3 and His-5) with others members being generated from the proteolytic cleavage of these (Table 3) (MacKay, Pollock et al. 1984, Troxler, Offner et al. 1990). Along with the capability of

inhibiting the growth of *Candida* species, they have other functions like regulating oral haemostasis and bonding of metal ions in saliva (Bercier, Al-Hashimi et al. 1999, Oudhoff, van den Keijbus et al. 2009). Histatins have high affinity for enamel surfaces and play a role in the formation of acquired enamel pellicle (Richardson, Johnsson et al. 1993). Their antifungal mechanism has a few phases; bonding to the specific membrane, transport through membrane, inhibition of mitochondrial respiration by forming reactive oxygen species, entering the cell by mobilisation of ions (K^+ , Mg^{2+}) and causing cell death (Xu, Levitz et al. 1991).

Oral candidiasis is a common infection in the human oral cavity associated with trauma or in immunocompromised patients due to low salivary flow (Sjorgren's syndrome). In these situations, histatins play an active positive role. *In-vitro*, Hst-5 has been shown to inhibit *Candida* species (*Candida albicans*, *Candida glabrata*, *Candida krusei*, and *Cryptococcus neoformans*) at physiological concentration (15-30 μ M) (Raj, Edgerton et al. 1990). Another study demonstrated that Hst M (middle portion of Hst-3) has the same candida-cidal activity as the full length molecule and this indicates the potential future use of short length antifungal peptides for oral ointments (Raj, Edgerton et al. 1990). Common cause of biofilm in dental prosthesis is by colonization of *Candida* and Hst-5 has showed potent limiting effect on biofilm in comparison to chlorhexidene (Pusateri, Monaco et al. 2009). A promising antimicrobial peptide appears to be the histatin 5 12-mer P113 (Demegen) which works as a mouth rinse for oral candidiasis in patients with human immuno deficiency virus HIV (Gorr 2009, Gorr 2011).

3.3. Cathelicidins (LL- 37)

Cathelicidins (LL37) are AMPs from the family of α -helical peptides without cysteine and located at the carboxyl terminus of a 15-18 kDa highly conserved cathepsin-L-inhibitor (cathelin)-like domain (Lehrer and Ganz 2002, Kosciuczuk, Lisowski et al. 2012). Cathelicidins only have one delegate in humans in the oral cavity and respiratory tract) which is known as human cationic antimicrobial peptide (hCAP18) (Murakami, Ohtake et al. 2002, Tecle, Tripathi et al. 2010). They are synthesized and stored in cells as 2 -domain proteins and when required are split by proteases to produce a cathelin protein and an antimicrobial peptide. They derive their name from the first two residues at the N-terminus (Leucine, Leucine) and contain 37 amino acids (Zanetti, Gennaro et al. 2002). LL37/hCAP18 has the function of stimulation of monocytes, neutrophils, mast cells and T-cells. Various studies have demonstrated the capability of LL37/hCAP18 as a potent antimicrobial against many gram-negative and positive bacteria, fungi, viruses and parasites (Tanaka, Miyasaki et al. 2000, Isogai, Isogai et al. 2003, López-García, Lee et al. 2005). LL37/hCAP18 neutralize bacteria very quickly by forming ionic channels in the cell membranes of the microorganisms and by ability to bind LPS of bacterial membranes (Zanetti, Gennaro et al. 2002). Turner, Cho et al. reported minimal inhibitory concentration (MIC) of LL37/hCAP18 range of less than 10 μ g/ml against microorganisms (Turner, Cho et al. 1998). Another study demonstrated the stronger killing action action of LL37/hCAP18 derived synthetic peptides against *Streptococcus sanguis* (isolated from behcet's disease) (Isogai, Hirata et al. 2003). In addition, Ouhara et al. chemically synthesized human b-defensin-1 (hBD1), hBD2, hBD3 and LL37 (CAP18) for their antimicrobial activity against oral bacteria (*Streptococcus mutans*, *S. sanguinis*, *S. Salivarius* and *S. mitis*) and demonstrated the high activity of LL37 against these pathogens (Ouhara, Komatsuzawa et al. 2005).

3.4. Adrenomedullin

Adrenomedullin is a cationic amphipathic peptide with one disulphide bond. It is a proteolytically processed 185 amino acid protein initially that is C-terminally amidated to produce the mature 52 amino acid adrenomedullin (Gorr 2009). This AMP is present in the gingival crevicular fluid and saliva. Although adrenomedullin is in both glandular and whole saliva, it is in large concentrations in whole saliva (Gorr 2009). This suggests that the oral epithelial cells donate to the salivary expression of adrenomedullin (Kapas, Pahal et al. 2004). It has been observed that the quantity of adrenomedullin is almost double in periodontally compromised areas than in healthy areas (Lundy, O'Hare et al. 2006).

3.5. Statherin

Statherin is a 5.4 kDa peptide belonging to the histatin/statherin family. It is believed that statherin and a basic histidine-rich peptide might have developed from a common ancestral gene (Dickinson, Ridall et al. 1987). Antimicrobial properties are observed in C-terminal peptide of the statherin (Kochanska, Kedzia et al. 2000). Statherin is found in saliva (Vitorino, Lobo et al. 2004, Wilmarth, Riviere et al. 2004, Denny, Hagen et al. 2008) and the gingival crevicular fluid (Pisano, Cabras et al. 2005). This AMP is secreted by the submandibular and the parotid glands and hinders the growth of anaerobic bacteria isolated from the oral cavity (Vitorino, Lobo et al. 2004, Wilmarth, Riviere et al. 2004, Denny, Hagen et al. 2008). Statherin also restrains the crystallization of calcium phosphate and hence may have a protective role against plaque formation (Wilmarth, Riviere et al. 2004, Denny, Hagen et al. 2008). The proteomic analysis of saliva acquired from patients with high and low numbers for bacterial adhesion and agglutination has revealed the potential of statherin to be utilized as a biomarker for infections in oral cavity (Rudney, Staikov et al. 2009).

3.6. C-C motif chemokine 28

This is a 128-amino acid peptide, which is principally expressed in a variety of epithelial cells, including salivary glands, and is observed in saliva (Denny, Hagen et al. 2008). The C-C motif chemokine 28 acts both as a broad-spectral antimicrobial agent and also as a chemokine (Gorr 2009). A C-terminal 28 amino peptide has similarities with histatin 5 and this peptide is salt sensitive, and increases the permeability of cell membrane, as has been noted for other cationic AMPs (Hieshima, Ohtani et al. 2003).

3.7. Azurocidin

Human saliva proteomic analysis helped in the identification of azurocidin, which is a 37 kDa cationic antimicrobial protein expressed in azurophil granules of neutrophils (1264,55). Azurocidin is a 251- amino acid protein has strong antibacterial properties towards gram-negative bacteria due to having strong affinity for lipopolysaccharide (Gorr 2009, Dhaifalah, Andrys et al. 2014). The two cysteine residues in positions 52 and 68 are thought to be essential for the antibacterial activity (Soehnlein and Lindbom 2009).

3.8. Neuropeptides

Gingival crevicular fluid contains the neuropeptides, calcitonin gene related peptide and substance P (Awawdeh, Lundy et al. 2002). In addition to these peptides, the neuropeptide Y and vasoactive intestinal peptide are also expressed and present in salivary fluids (Dawidson, Blom et al. 1997). However, their antimicrobial role is extremely limited since their concentrations varying from 2-45 pg/ml are lower by several orders of magnitude than the minimum inhibitory concentrations required to be effective against *Candida albicans* and bacteria (El Karim, Linden et al. 2008).

3.9. Role of AMPs in oral diseases

The exposure of gingival epithelial cells with bacteria related to periodontitis results in the production of β -defensins and LL-37 (Gorr 2009). Around twenty genetic disorders connected with periodontal disease have been identified to date (Hart and Atkinson 2007). Some of these disorders are associated with alterations in the AMP expression, which potentially increases the susceptibility to bacterial infections (Gorr 2009). It has been shown that conditions of severe congenital neutropenia (Marbus Kostman disease) are associated with severe irreversible periodontitis (Putsep, Carlsson et al. 2002). These patients have insufficient LL-37 in neutrophils, saliva and plasma. Also the α -defensins are markedly reduced (to about 30% of normal) while the lactoferrin content in plasma remains normal (Putsep, Carlsson et al. 2002). Individuals suffering from Marbus Kostman when treated with granulocyte-colony stimulating factor demonstrate regular neutrophil count but still lack LL-37 and continue to suffer from advanced periodontal disease (Carlsson, Thilander et al. 1967, Putsep, Carlsson et al. 2002). It has been observed that bone marrow transplantation in a patient resulted in the restoration of both neutrophils and LL-37 to normal levels. While this proved that LL-37 is related to periodontal disease, normal levels were not enough to prevent or restore the periodontal disease alone (Bachrach, Chaushu et al. 2006, Gorr 2009). Periodontal disease is also common in children with Down's Syndrome (Trisomy 21) (Orner 1976). Mucin -7 and lactoferrin are other AMPs that are associated with periodontal disease. In *A. actinomycetemcomitans*-associated periodontitis, the levels of mucin -7 are decreased three fold when compared with disease free patients (Groenink, Walgreen-Weterings et al. 1999). Lactoferrin levels are shown to be within normal ranges, but the protein is iron saturated, indicating a reduction in the antimicrobial properties in patients with periodontitis (Groenink, Walgreen-Weterings et al. 1999).

Other oral diseases and infections have also exhibited relations to the levels of expression of AMPs. Low levels of variety of AMPs, including lactoferrin and β -defensins 1 and 2 are associated with oral candidiasis (Tanida, Okamoto et al. 2003). Remarkable variations in susceptibility to AMPs hBD3 and LL-37 have been noted between different species of oral bacteria and differing strains of the same species (Ji, Hyun et al. 2007). A good example of this is the *Streptococcus Gordonii* M5 that is weakly susceptible to both AMP hBD3 and LL-37, while *Streptococcus. Gordonii* 10558 is highly susceptible. *P. Gingivalis* 33277, by contrast, is less susceptible to LL-37 but greatly susceptible to death by hBD3 (Ji, Hyun et al. 2007). Haim–Munk syndrome and the Papillon–Lefe`vre syndrome are induced by allelic mutations of the cathepsin C gene, CTSC 1 and identified by severe periodontitis and palmoplantar keratoderma (Hart, Hart et al. 2000). Although, patients with Papillon–Lefe`vre syndrome express normal levels of the cathelicidin precursor, very little is processed to the mature LL-37 peptide. Similar to Morbus Kostman, it is plausible that the decreased levels of LL-37 results in occurrence of periodontitis in patients with Papillon–Lefe`vre syndrome (de Haar, Hiemstra et al. 2006).

The interrelation of AMPs expression levels and occurrence of caries has been difficult to establish. Development of caries in children has been linked with the low-level expression of α -defensins (human neutrophil peptides 1–3) (Tao, Jurevic et al. 2005). However, due to the fact that caries is observed at broad variation in α -defensin expression levels, it cannot be definitely established whether α -defensin expression is accurately predictive of development of future caries (Dale, Tao et al. 2006). Also, salivary peroxidase and lactoferrin have not shown correlation with occurrence of caries in clinical studies carried out in children (Kirstila, Hakkinen et al. 1998) and adults (Grahn, Tenovuo et al. 1988). The wide variety and range of AMP expression levels between study subjects is possibly one of the strong reasons for the complication in relating single point analysis of AMPs with oral disease

(Tenovuo, Grahn et al. 1987). It is already known that salivary peptide levels between patients can differ about 100-fold (levels normalized to total salivary protein (Tao, Jurevic et al. 2005). This makes it very challenging to express exact or normal values for individual AMPs. A multiplex investigative and analytical approach towards antimicrobial protein expression in healthy and diseased individuals with the aim to recognize AMP signatures would potentially result in higher predictive/diagnostic power.

4. Conclusions

A wide range of AMPs with miscellaneous functions have been discovered in the oral tissues and secretions. The protective role played by these peptides against microbes entering the oral cavity results in effective fight against infections. The interest in the potential use of AMPs as a therapeutic regimen is due to their wide range of efficacy and low rates of induced resistance owing to the co-evolution of pathogens and the host AMPs. After reviewing the literature we can conclude that these AMPs have promising potential to be used against oral microbes in order control their growth and biofilm formation. There are many challenges that need to be overcome in order to design and synthesize AMPs that have the ability to withstand the unique and harsh oral environment. AMPs are expected in the future to be used as models for designing effective oral microbial antibiotics.

Conflict of interest

None

References

Abiko, Y., Y. Jinbu, T. Noguchi, M. Nishimura, K. Kusano, P. Amaratunga, T. Shibata and T. Kaku 2002. Upregulation of human beta-defensin 2 peptide expression in oral lichen planus, leukoplakia and candidiasis. an immunohistochemical study. *Pathology-Research and Practice* 198(8): 537-542.

Abiko, Y., M. Saitoh, M. Nishimura, M. Yamazaki, D. Sawamura and T. Kaku 2007. Role of beta-defensins in oral epithelial health and disease. *Med Mol Morphol* 40(4): 179-184.

Adonogianaki, E., J. Mooney and D. F. Kinane 1996. Detection of stable and active periodontitis sites by clinical assessment and gingival crevicular acute-phase protein levels. *J Periodontal Res* 31(2): 135-143.

Adonogianaki, E., N. A. Moughal and D. F. Kinane 1993. Lactoferrin in the gingival crevice as a marker of polymorphonuclear leucocytes in periodontal diseases. *J Clin Periodontol* 20(1): 26-31.

Aguilera, O., M. T. Andres, J. Heath, J. F. Fierro and C. W. Douglas 1998. Evaluation of the antimicrobial effect of lactoferrin on *Porphyromonas gingivalis*, *Prevotella intermedia* and *Prevotella nigrescens*. *FEMS Immunol Med Microbiol* 21(1): 29-36.

Akalin, F. A., S. Bulut and E. Yavuzylmaz 1993. beta 2-Microglobulin levels in serum and saliva of patients with juvenile periodontitis. *J Nihon Univ Sch Dent* 35(4): 230-234.

Allaker, R. P., C. Zihni and S. Kapas 1999. An investigation into the antimicrobial effects of adrenomedullin on members of the skin, oral, respiratory tract and gut microflora. *FEMS Immunol Med Microbiol* 23(4): 289-293.

Allgrove, J. E., E. Gomes, J. Hough and M. Gleeson 2008. Effects of exercise intensity on salivary antimicrobial proteins and markers of stress in active men. *J Sports Sci* 26(6): 653-661.

Alves, D. and M. Olivia Pereira 2014. Mini-review: Antimicrobial peptides and enzymes as promising candidates to functionalize biomaterial surfaces. *Biofouling* 30(4): 483-499.

- Amerongen, A. and E. Veerman 2002. Saliva—the defender of the oral cavity. *Oral diseases* 8(1): 12-22.
- Ashby, M., A. Petkova and K. Hilpert 2014. Cationic antimicrobial peptides as potential new therapeutic agents in neonates and children: a review. *Curr Opin Infect Dis* 27(3): 258-267.
- Awawdeh, L., F. T. Lundy, C. Shaw, P. J. Lamey, G. J. Linden and J. G. Kennedy 2002. Quantitative analysis of substance P, neurokinin A and calcitonin gene-related peptide in pulp tissue from painful and healthy human teeth. *Int Endod J* 35(1): 30-36.
- Bachrach, G., G. Chaushu, M. Zigmond, E. Yefenof, A. Stabholz, J. Shapira, J. Merrick and S. Chaushu 2006. Salivary LL-37 secretion in individuals with Down syndrome is normal. *J Dent Res* 85(10): 933-936.
- Bercier, J. G., I. Al-Hashimi, N. Haghighat, T. D. Rees and F. G. Oppenheim 1999. Salivary histatins in patients with recurrent oral candidiasis. *J Oral Pathol Med* 28(1): 26-29.
- Bocchinfuso, G., A. Palleschi, B. Orioni, G. Grande, F. Formaggio, C. Toniolo, Y. Park, K. S. Hahm and L. Stella 2009. Different mechanisms of action of antimicrobial peptides: insights from fluorescence spectroscopy experiments and molecular dynamics simulations. *J Pept Sci* 15(9): 550-558.
- Brogden, K. A. 2005. Antimicrobial peptides: pore formers or metabolic inhibitors in bacteria?" *Nature Reviews Microbiology* 3(3): 238-250.
- Bulet, P., J. Dimarcq, C. Hetru, M. Lagueux, M. Charlet, G. Hegy, A. Van Dorsselaer and J. Hoffmann 1993. A novel inducible antibacterial peptide of *Drosophila* carries an O-glycosylated substitution. *Journal of Biological Chemistry* 268(20): 14893-14897.
- Cardot Martin, E., A. Michel, B. Raynal, C. Badiou, F. Laurent, F. Vandenesch, J. Etienne, G. Lina and O. Dumitrescu 2015. Community-acquired methicillin-resistant *Staphylococcus aureus* strain USA300 resists staphylococcal protein A modulation by antibiotics and antimicrobial peptides. *Int J Antimicrob Agents* 45(1): 19-24.

Carlsson, G. E., H. Thilander and B. Hedegard 1967. Histologic changes in the upper alveolar process after extractions with or without insertion of an immediate full denture. *Acta Odontol Scand* 25(1): 21-43.

Dale, B. A. and L. P. Fredericks 2005. Antimicrobial peptides in the oral environment: expression and function in health and disease. *Current issues in molecular biology* 7(2): 119.

Dale, B. A. and S. Krisanaprakornkit 2001. Defensin antimicrobial peptides in the oral cavity. *Journal of oral pathology & medicine* 30(6): 321-327.

Dale, B. A., R. Tao, J. R. Kimball and R. J. Jurevic 2006. Oral antimicrobial peptides and biological control of caries. *BMC Oral Health* 6(Suppl 1): S13.

Dale, B. A., R. Tao, J. R. Kimball and R. J. Jurevic 2006. Oral antimicrobial peptides and biological control of caries. *BMC Oral Health* 6 Suppl 1: S13.

Dawidson, I., M. Blom, T. Lundeberg, E. Theodorsson and B. Angmar-Mansson 1997. Neuropeptides in the saliva of healthy subjects. *Life Sci* 60(4-5): 269-278.

de Haar, S. F., P. S. Hiemstra, M. T. van Steenberghe, V. Everts and W. Beertsen 2006. Role of polymorphonuclear leukocyte-derived serine proteinases in defense against *Actinobacillus actinomycetemcomitans*. *Infect Immun* 74(9): 5284-5291.

de Sousa-Pereira, P., F. Amado, J. Abrantes, R. Ferreira, P. J. Esteves and R. Vitorino 2013. An evolutionary perspective of mammal salivary peptide families: Cystatins, histatins, statherin and PRPs. *Archives of oral biology* 58(5): 451-458.

Denny, P., F. K. Hagen, M. Hardt, L. Liao, W. Yan, M. Arellanno, S. Bassilian, G. S. Bedi, P. Boontheung, D. Cociorva, C. M. Delahunty, T. Denny, J. Dunsmore, K. F. Faull, J. Gilligan, M. Gonzalez-Begne, F. Halgand, S. C. Hall, X. Han, B. Henson, J. Hewel, S. Hu, S. Jeffrey, J. Jiang, J. A. Loo, R. R. Ogorzalek Loo, D. Malamud, J. E. Melvin, O. Miroshnychenko, M. Navazesh, R. Niles, S. K. Park, A. Prakobphol, P. Ramachandran, M. Richert, S. Robinson, M. Sondej, P. Souda, M. A. Sullivan, J. Takashima, S. Than, J. Wang,

- J. P. Whitelegge, H. E. Witkowska, L. Wolinsky, Y. Xie, T. Xu, W. Yu, J. Ytterberg, D. T. Wong, J. R. Yates, 3rd and S. J. Fisher 2008. The proteomes of human parotid and submandibular/sublingual gland salivas collected as the ductal secretions. *J Proteome Res* 7(5): 1994-2006.
- Dhaifalah, I., C. Andrys, M. Drahosova, I. Musilova, Z. Adamik and M. Kacerovsky 2014. Azurocidin levels in maternal serum in the first trimester can predict preterm prelabor rupture of membranes. *J Matern Fetal Neonatal Med* 27(5): 511-515.
- Diamond, G. and L. Ryan 2011. Beta-defensins: what are they really doing in the oral cavity?" *Oral Dis* 17(7): 628-635.
- Dickinson, D. P., A. L. Ridall and M. J. Levine 1987. Human submandibular gland statherin and basic histidine-rich peptide are encoded by highly abundant mRNA's derived from a common ancestral sequence. *Biochem Biophys Res Commun* 149(2): 784-790.
- Dunsche, A., Y. Açil, R. Siebert, J. Harder, J. M. Schröder and S. Jepsen 2001. Expression profile of human defensins and antimicrobial proteins in oral tissues. *Journal of oral pathology & medicine* 30(3): 154-158.
- El Karim, I. A., G. J. Linden, D. F. Orr and F. T. Lundy 2008. Antimicrobial activity of neuropeptides against a range of micro-organisms from skin, oral, respiratory and gastrointestinal tract sites. *J Neuroimmunol* 200(1-2): 11-16.
- Epand, R. M. and H. J. Vogel 1999. Diversity of antimicrobial peptides and their mechanisms of action. *Biochim Biophys Acta* 1462(1-2): 11-28.
- Fanali, C., R. Inzitari, T. Cabras, E. Pisano, M. Castagnola, R. Celletti, A. Manni and I. Messina 2007. alpha-Defensin levels in whole saliva of totally edentulous subjects. *International journal of immunopathology and pharmacology* 21(4): 845-849.

Gabay, J. E., R. W. Scott, D. Campanelli, J. Griffith, C. Wilde, M. N. Marra, M. Seeger and C. F. Nathan 1989. Antibiotic proteins of human polymorphonuclear leukocytes. *Proceedings of the National Academy of Sciences* 86(14): 5610-5614.

Ganz, T. 2003. Defensins: antimicrobial peptides of innate immunity. *Nature Reviews Immunology* 3(9): 710-720.

Ganz, T., M. E. Selsted, D. Szklarek, S. Harwig, K. Daher, D. F. Bainton and R. I. Lehrer 1985. Defensins. Natural peptide antibiotics of human neutrophils. *Journal of Clinical Investigation* 76(4): 1427.

Gennaro, R., M. Zanetti, M. Benincasa, E. Podda and M. Miani 2002. Pro-rich antimicrobial peptides from animals: structure, biological functions and mechanism of action. *Curr Pharm Des* 8(9): 763-778.

Gomes Pde, S. and M. H. Fernandes 2010. Defensins in the oral cavity: distribution and biological role. *J Oral Pathol Med* 39(1): 1-9.

Gordon, Y. J., L. C. Huang, E. G. Romanowski, K. A. Yates, R. J. Proske and A. M. McDermott 2005. Human cathelicidin LL-37, a multifunctional peptide, is expressed by ocular surface epithelia and has potent antibacterial and antiviral activity. *Curr Eye Res* 30(5): 385-394.

Gordon, Y. J., E. G. Romanowski and A. M. McDermott 2005. A review of antimicrobial peptides and their therapeutic potential as anti-infective drugs. *Current eye research* 30(7): 505-515.

Gorr, S.-U. 2011. Antimicrobial peptides in periodontal innate defense."

Gorr, S. U. 2009. Antimicrobial peptides of the oral cavity. *Periodontol* 2000 51: 152-180.

Grahn, E., J. Tenovu, O. P. Lehtonen, E. Eerola and P. Vilja 1988. Antimicrobial systems of human whole saliva in relation to dental caries, cariogenic bacteria, and gingival inflammation in young adults. *Acta Odontol Scand* 46(2): 67-74.

- Greer, A., C. Zenobia and R. P. Darveau 2013. Defensins and LL-37: a review of function in the gingival epithelium. *Periodontol* 2000 63(1): 67-79.
- Groenink, J., E. Walgreen-Weterings, K. Nazmi, J. G. Bolscher, E. C. Veerman, A. J. van Winkelhoff and A. V. Nieuw Amerongen 1999. Salivary lactoferrin and low-Mr mucin MG2 in *Actinobacillus actinomycetemcomitans*-associated periodontitis. *J Clin Periodontol* 26(5): 269-275.
- Hancock, R. E. and R. Lehrer 1998. Cationic peptides: a new source of antibiotics. *Trends in biotechnology* 16(2): 82-88.
- Hancock, R. E. and H.-G. Sahl 2006. Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies. *Nature biotechnology* 24(12): 1551-1557.
- Haney, E. F., A. P. Petersen, C. K. Lau, W. Jing, D. G. Storey and H. J. Vogel 2013. Mechanism of action of puroidoline derived tryptophan-rich antimicrobial peptides. *Biochim Biophys Acta* 1828(8): 1802-1813.
- Harris, F., S. R. Dennison and D. A. Phoenix 2009. Anionic antimicrobial peptides from eukaryotic organisms. *Current Protein and Peptide Science* 10(6): 585-606.
- Hart, T. C. and J. C. Atkinson 2007. Mendelian forms of periodontitis. *Periodontol* 2000 45: 95-112.
- Hart, T. C., P. S. Hart, M. D. Michalec, Y. Zhang, E. Firatli, T. E. Van Dyke, A. Stabholz, A. Zlotogorski, L. Shapira and W. A. Soslone 2000. Haim-Munk syndrome and Papillon-Lefevre syndrome are allelic mutations in cathepsin C. *J Med Genet* 37(2): 88-94.
- Hieshima, K., H. Ohtani, M. Shibano, D. Izawa, T. Nakayama, Y. Kawasaki, F. Shiba, M. Shiota, F. Katou, T. Saito and O. Yoshie 2003. CCL28 has dual roles in mucosal immunity as a chemokine with broad-spectrum antimicrobial activity. *J Immunol* 170(3): 1452-1461.
- Isogai, E., M. Hirata, H. Isogai, K. Matuo, K. Kimura, K. Yokota, K. Oguma, M. Tojo, F. Kaneko and S. Kotake 2003. Antimicrobial Activity of Synthetic Human CAP18 Peptides to

Streptococcus sanguis Isolated from Patients with Behçet's Disease. Adamantiades-Behçet's Disease, Springer: 195-200.

Isogai, E., H. Isogai, K. Matuo, K. Hirose, Y. Kowashi, K. Okumuara and M. Hirata 2003. Sensitivity of genera *Porphyromonas* and *Prevotella* to the bactericidal action of C-terminal domain of human CAP18 and its analogues. *Oral microbiology and immunology* 18(5): 329-332.

Ji, S., J. Hyun, E. Park, B. L. Lee, K. K. Kim and Y. Choi 2007. Susceptibility of various oral bacteria to antimicrobial peptides and to phagocytosis by neutrophils. *J Periodontal Res* 42(5): 410-419.

Kang, S. J., S. J. Park, T. Mishig-Ochir and B. J. Lee 2014. Antimicrobial peptides: therapeutic potentials. *Expert Rev Anti Infect Ther* 12(12): 1477-1486.

Kapas, S., K. Pahal, A. T. Cruchley, E. Hagi-Pavli and J. P. Hinson 2004. Expression of adrenomedullin and its receptors in human salivary tissue. *J Dent Res* 83(4): 333-337.

Kirstila, V., P. Hakkinen, H. Jentsch, P. Vilja and J. Tenovuo 1998. Longitudinal analysis of the association of human salivary antimicrobial agents with caries increment and cariogenic micro-organisms: a two-year cohort study. *J Dent Res* 77(1): 73-80.

Kochanska, B., A. Kedzia, W. Kamysz, Z. Mackiewicz and G. Kupryszewski 2000. The effect of statherin and its shortened analogues on anaerobic bacteria isolated from the oral cavity. *Acta Microbiol Pol* 49(3-4): 243-251.

Koczulla, A. R. and R. Bals 2003. Antimicrobial peptides: current status and therapeutic potential. *Drugs* 63(4): 389-406.

Kosciuczuk, E. M., P. Lisowski, J. Jarczak, N. Strzalkowska, A. Jozwik, J. Horbanczuk, J. Krzyzewski, L. Zwierzchowski and E. Bagnicka 2012. Cathelicidins: family of antimicrobial peptides. A review. *Mol Biol Rep* 39(12): 10957-10970.

- Krisanaprakornkit, S., A. Weinberg, C. N. Perez and B. A. Dale 1998. Expression of the peptide antibiotic human β -defensin 1 in cultured gingival epithelial cells and gingival tissue. *Infection and immunity* 66(9): 4222-4228.
- Lehrer, R. I. and T. Ganz 2002. Cathelicidins: a family of endogenous antimicrobial peptides. *Current opinion in hematology* 9(1): 18-22.
- Liu, L., C. Zhao, H. H. Heng and T. Ganz 1997. The human β -defensin-1 and α -defensins are encoded by adjacent genes: two peptide families with differing disulfide topology share a common ancestry. *Genomics* 43(3): 316-320.
- López-García, B., P. Lee, K. Yamasaki and R. L. Gallo 2005. Anti-fungal activity of cathelicidins and their potential role in *Candida albicans* skin infection. *The Journal of investigative dermatology* 125(1): 108-115.
- Lundy, F. T., M. M. O'Hare, B. M. McKibben, C. R. Fulton, J. E. Briggs and G. J. Linden 2006. Radioimmunoassay quantification of adrenomedullin in human gingival crevicular fluid. *Arch Oral Biol* 51(4): 334-338.
- MacKay, B., J. Pollock, V. Iacono and B. Baum 1984. Isolation of milligram quantities of a group of histidine-rich polypeptides from human parotid saliva. *Infection and immunity* 44(3): 688-694.
- Melo, M. N. and M. A. Castanho 2012. The Mechanism of Action of Antimicrobial Peptides: Lipid Vesicles vs. Bacteria. *Front Immunol* 3: 236.
- Meyer, J. E. and J. Harder 2007. Antimicrobial peptides in oral cancer. *Curr Pharm Des* 13(30): 3119-3130.
- Murakami, M., T. Ohtake, R. Dorschner and R. Gallo 2002. Cathelicidin antimicrobial peptides are expressed in salivary glands and saliva. *Journal of dental research* 81(12): 845-850.

- Orner, G. 1976. Periodontal disease among children with Down's syndrome and their siblings. *J Dent Res* 55(5): 778-782.
- Oudhoff, M. J., P. A. van den Keijbus, K. L. Kroeze, K. Nazmi, S. Gibbs, J. G. Bolscher and E. C. Veerman 2009. Histatins enhance wound closure with oral and non-oral cells. *J Dent Res* 88(9): 846-850.
- Ouhara, K., H. Komatsuzawa, S. Yamada, H. Shiba, T. Fujiwara, M. Ohara, K. Sayama, K. Hashimoto, H. Kurihara and M. Sugai 2005. Susceptibilities of periodontopathogenic and cariogenic bacteria to antibacterial peptides, β -defensins and LL37, produced by human epithelial cells. *Journal of Antimicrobial Chemotherapy* 55(6): 888-896.
- Pisano, E., T. Cabras, C. Montaldo, V. Piras, R. Inzitari, C. Olmi, M. Castagnola and I. Messana 2005. Peptides of human gingival crevicular fluid determined by HPLC-ESI-MS. *European journal of oral sciences* 113(6): 462-468.
- Pusateri, C. R., E. A. Monaco and M. Edgerton 2009. Sensitivity of *Candida albicans* biofilm cells grown on denture acrylic to antifungal proteins and chlorhexidine. *Archives of oral biology* 54(6): 588-594.
- Putsep, K., G. Carlsson, H. G. Boman and M. Andersson 2002. Deficiency of antibacterial peptides in patients with morbus Kostmann: an observation study. *Lancet* 360(9340): 1144-1149.
- Quinones-Mateu, M. E., M. M. Lederman, Z. Feng, B. Chakraborty, J. Weber, H. R. Rangel, M. L. Marotta, M. Mirza, B. Jiang, P. Kiser, K. Medvik, S. F. Sieg and A. Weinberg 2003. Human epithelial beta-defensins 2 and 3 inhibit HIV-1 replication. *AIDS* 17(16): F39-48.
- Raj, P. A., M. Edgerton and M. Levine 1990. Salivary histatin 5: dependence of sequence, chain length, and helical conformation for candidacidal activity. *Journal of Biological Chemistry* 265(7): 3898-3905.

- Richardson, C., M. Johnsson, P. Raj, M. Levine and G. Nancollas 1993. The influence of histatin-5 fragments on the mineralization of hydroxyapatite. *Archives of oral biology* 38(11): 997-1002.
- Rudney, J. D., R. K. Staikov and J. D. Johnson 2009. Potential biomarkers of human salivary function: a modified proteomic approach. *Arch Oral Biol* 54(1): 91-100.
- Selsted, M. E., S. Harwig, T. Ganz, J. W. Schilling and R. Lehrer 1985. Primary structures of three human neutrophil defensins. *Journal of Clinical Investigation* 76(4): 1436.
- Sewald, N. and H.-D. Jakubke 2002. *Peptides: chemistry and biology*, Wiley-Vch Weinheim.
- Shai, Y. 2002. Mode of action of membrane active antimicrobial peptides. *Biopolymers* 66(4): 236-248.
- Sinha, S., N. Cheshenko, R. I. Lehrer and B. C. Herold 2003. NP-1, a rabbit alpha-defensin, prevents the entry and intercellular spread of herpes simplex virus type 2. *Antimicrob Agents Chemother* 47(2): 494-500.
- Soehnlein, O. and L. Lindbom 2009. Neutrophil-derived azurocidin alarms the immune system. *J Leukoc Biol* 85(3): 344-351.
- Tanaka, D., K. Miyasaki and R. Lehrer 2000. Sensitivity of *Actinobacillus actinomycetemcomitans* and *Campylobacter* spp. to the bactericidal action of LL-37: a cathelicidin found in human leukocytes and epithelium. *Oral microbiology and immunology* 15(4): 226-231.
- Tanida, T., T. Okamoto, A. Okamoto, H. Wang, T. Hamada, E. Ueta and T. Osaki 2003. Decreased excretion of antimicrobial proteins and peptides in saliva of patients with oral candidiasis. *J Oral Pathol Med* 32(10): 586-594.
- Tao, R., R. J. Jurevic, K. K. Coulton, M. T. Tsutsui, M. C. Roberts, J. R. Kimball, N. Wells, J. Berndt and B. A. Dale 2005. Salivary antimicrobial peptide expression and dental caries experience in children. *Antimicrob Agents Chemother* 49(9): 3883-3888.

- Teele, T., S. Tripathi and K. L. Hartshorn 2010. Review: Defensins and cathelicidins in lung immunity. *Innate Immun* 16(3): 151-159.
- Tenovuo, J., E. Grahn, O. P. Lehtonen, T. Hyyppä, L. Karhuvaara and P. Vilja 1987. Antimicrobial factors in saliva: ontogeny and relation to oral health. *J Dent Res* 66(2): 475-479.
- Tomasinsig, L., B. Skerlavaj, M. Scarsini, F. Guida, R. Piccinini, A. Tossi and M. Zanetti 2012. Comparative activity and mechanism of action of three types of bovine antimicrobial peptides against pathogenic *Prototheca* spp. *J Pept Sci* 18(2): 105-113.
- Troxler, R., G. Offner, T. Xu, J. Vanderspek and F. Oppenheim 1990. Structural relationship between human salivary histatins. *Journal of dental research* 69(1): 2-6.
- Turner, J., Y. Cho, N.-N. Dinh, A. J. Waring and R. I. Lehrer 1998. Activities of LL-37, a cathelin-associated antimicrobial peptide of human neutrophils. *Antimicrobial agents and chemotherapy* 42(9): 2206-2214.
- Vale, N., L. Aguiar and P. Gomes 2014. Antimicrobial peptides: a new class of antimalarial drugs?" *Front Pharmacol* 5: 275.
- van 't Hof, W., E. C. Veerman, E. J. Helmerhorst and A. V. Amerongen 2001. Antimicrobial peptides: properties and applicability. *Biol Chem* 382(4): 597-619.
- Vitorino, R., M. J. Lobo, A. J. Ferrer-Correia, J. R. Dubin, K. B. Tomer, P. M. Domingues and F. M. Amado 2004. Identification of human whole saliva protein components using proteomics. *Proteomics* 4(4): 1109-1115.
- Vos, W. M., O. P. Kuipers, J. R. Meer and R. J. Siezen 1995. Maturation pathway of nisin and other lantibiotics: post-translationally modified antimicrobial peptides exported by Gram-positive bacteria. *Molecular microbiology* 17(3): 427-437.
- Wang, G. 2014. Human Antimicrobial Peptides and Proteins. *Pharmaceuticals* 7(5): 545-594.

- Wang, W., S. M. Owen, D. L. Rudolph, A. M. Cole, T. Hong, A. J. Waring, R. B. Lal and R. I. Lehrer 2004. Activity of alpha- and theta-defensins against primary isolates of HIV-1. *J Immunol* 173(1): 515-520.
- White, S. H., W. C. Wimley and M. E. Selsted 1995. Structure, function, and membrane integration of defensins. *Current opinion in structural biology* 5(4): 521-527.
- Wilde, C., J. Griffith, M. Marra, J. Snable and R. Scott 1989. Purification and characterization of human neutrophil peptide 4, a novel member of the defensin family. *Journal of Biological Chemistry* 264(19): 11200-11203.
- Wilmarth, P. A., M. A. Riviere, D. L. Rustvold, J. D. Lauten, T. E. Madden and L. L. David 2004. Two-dimensional liquid chromatography study of the human whole saliva proteome. *J Proteome Res* 3(5): 1017-1023.
- Xu, T., S. Levitz, R. Diamond and F. Oppenheim 1991. Anticandidal activity of major human salivary histatins. *Infection and immunity* 59(8): 2549-2554.
- Yang, D., A. Biragyn, D. M. Hoover, J. Lubkowski and J. J. Oppenheim 2004. Multiple roles of antimicrobial defensins, cathelicidins, and eosinophil-derived neurotoxin in host defense. *Annu Rev Immunol* 22: 181-215.
- Yang, D., A. Biragyn, L. W. Kwak and J. J. Oppenheim 2002. Mammalian defensins in immunity: more than just microbicidal. *Trends Immunol* 23(6): 291-296.
- Yasin, B., W. Wang, M. Pang, N. Cheshenko, T. Hong, A. J. Waring, B. C. Herold, E. A. Wagar and R. I. Lehrer 2004. Theta defensins protect cells from infection by herpes simplex virus by inhibiting viral adhesion and entry. *J Virol* 78(10): 5147-5156.
- Yoshio, H., H. Lagercrantz, G. H. Gudmundsson and B. Agerberth 2004. First line of defense in early human life. *Seminars in perinatology*, Elsevier.

Zanetti, M., R. Gennaro, M. Scocchi and B. Skerlavaj 2002. Structure and biology of cathelicidins. *The Biology and Pathology of Innate Immunity Mechanisms*, Springer: 203-218.

Zasloff, M. 2002. Antimicrobial peptides of multicellular organisms. *Nature* 415(6870): 389-395.

Figure Legends

Figure 1 Illustration representing model of antimicrobial peptides for killing microorganisms. (a) Barrel-stave model, (b) carpet model, (c) toroidal model.

Figure 1 Molecular structure of human α -defensins with their cysteine consensus.

Figure 2 Molecular structures of β - defensins.

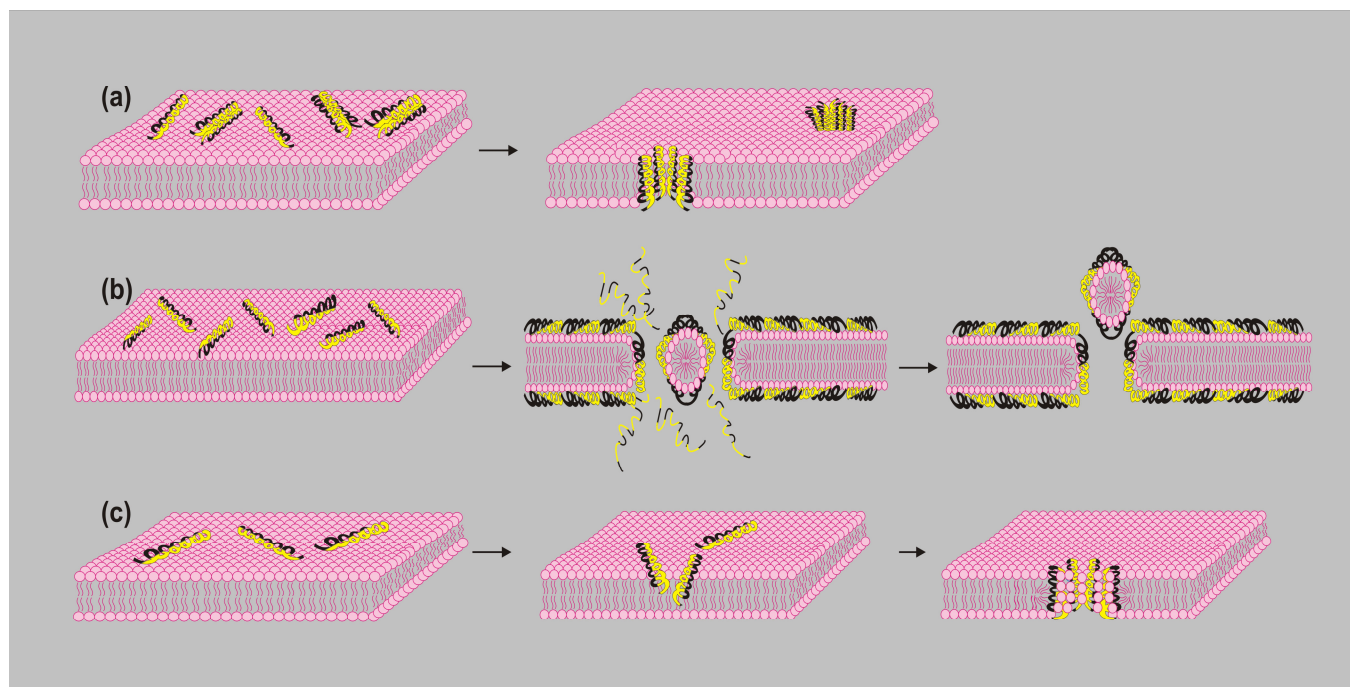


Figure 1 Illustration representing model of antimicrobial peptides for killing microorganisms. (a) Barrel-stave model, (b) carpet model, (c) toroidal model.

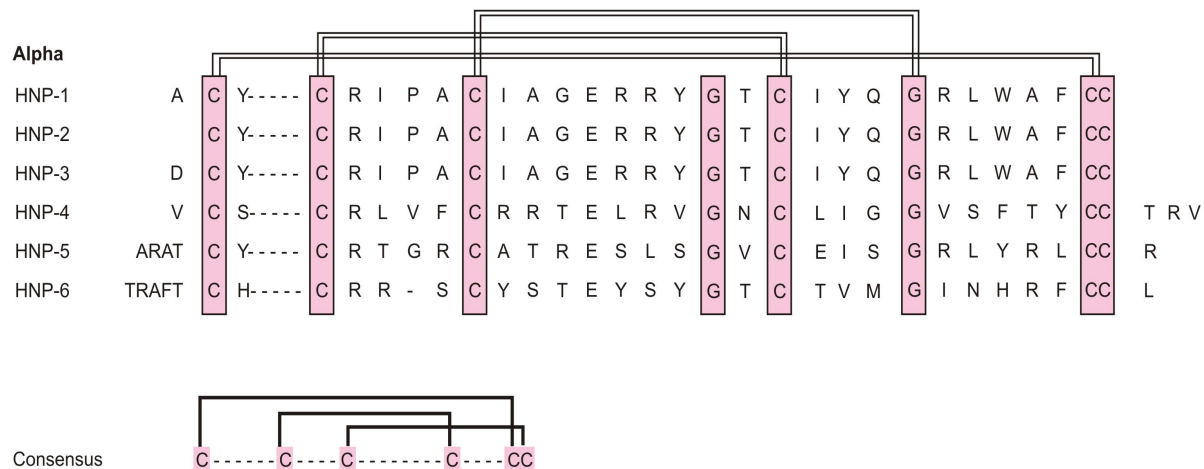


Figure 3 Molecular structure of human α -defensins with their cysteine consensus.

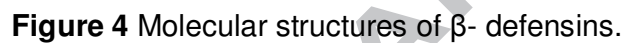


Table 1 Representation of Antimicrobial peptides classification on different basis.

Classes	Comments
Anionic peptides	They are small, rich in glutamic acids and aspartic acids, present in human, cattle and sheep.
Linear cationic α -helical peptides	They are short of cysteine and short peptides .e.g. LL37 from human.
Cationic peptides enriched for specific amino acids	They are proline rich peptides e.g. abaecin from honey bees.
Anionic and cationic peptides (contain cysteine and disulfide bonds)	They contain cysteins with one or more disulfide bonds e.g. protegrin from pigs, tachyplesins from horse crabs and α – β - defensins from humans, cattle, mice and pigs.
Anionic and cationic peptides fragments of larger proteins	They are similar to others AMPs but their role in innate immunity is not yet clear .e.g. lectoferricin from Lactoferrin and casocidin-I from human casein.

Table 2 Complete list of human oral antimicrobial peptides from Antimicrobial Peptide Database (APD)

Antimicrobial peptides	Year	Site of expression
α - Defensins (HNP-1)	1985	Neutrophils (azurophilic granules), gingival crevicular fluid and bone marrow
α - Defensins (HNP-2)	1985	Neutrophils (azurophilic granules), gingival crevicular fluid and bone marrow
α - Defensins (HNP-3)	1985	Neutrophils (azurophilic granules), gingival crevicular fluid and bone marrow
α - Defensins (HNP-4)	1989	Neutrophils
β - Defensins (hBD-1)	1995	Suprabasal layer of stratified epithelium and saliva
β - Defensins (hBD-2)	1997	Gingival epithelium and saliva
β - Defensins (hBD-3)	2001	Skin and salivary gland
Histatin-1	1988	Saliva (parotid and submandibular)
Histatin-3	1988	Saliva (parotid and submandibular)
Histatin-5	1988	Saliva (parotid and submandibular)
Adrenomedullin	1993	Epithelium
Cathelicidins (LL-37)	1995	Neutrophils, inflamed epithelia, submandibular glands and saliva

(<http://aps.unmc.edu/AP/>)

Table 3 Histatin Family with their proteolytic fragments.

Natural Histatins	Present	Sequences
In Saliva		
Histatin 1		DSpHEKRHHGYRRKFHEKHHSHREFPFYGDYGSNYLYDN
Histatin 3		DSHAKRHHGYKRKFHEKHHSHRGYRSNYLYDN
Histatin 5		DSHAKRHHGYKRKFHEKHHSHRGY
<i>Proteolytic fragments in saliva</i>		
Histatin 2		RKFHEKHHSHREFPFYGDYGSNYLYDN
Histatin 4		KFHEKHHSHRGYRSNYLYDN
Histatin 6		DSHAKRHHGYKRKFHEKHHSHRGYR
Histatin 7		RKFHEKHHSHRGY
Histatin 8		KFHEKHHSHRGY
Histatin 9		RKFHEKHHSHRGYR
Histatin 10		KFHEKHHSHRGYR
Histatin 11		KRHHGYKR
Histatin 12		KRHHGYK